**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 403/06, 417/14, 401/14, A61K 31/50 | A1

(11) International Publication Number: **WO 96/37489**

(43) International Publication Date: 28 November 1996 (28.11.96)

(21) International Application Number: PCT/JP96/01335

(22) International Filing Date: 21 May 1996 (21.05.96)

(30) Priority Data:
08/450,176 25 May 1995 (25.05.95) US

(71) Applicant: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

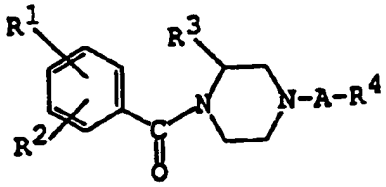
(72) Inventors: MATSUO, Masaaki; 4-12, Nakasakurazuka 5-chome, Toyonaka-shi, Osaka 560 (JP). HAGIWARA, Daijiro; 20-11, Kindacho 2-chome, Moriguchi-shi, Osaka 570 (JP). MANABE, Takashi; 1-2-103, Maruyamadai, Kawanishi-shi, Hyogo 666-01 (JP). KONISHI, Nobukiyo; 22-7, Aotanai, Nagaokakyo-shi, Kyoto 617 (JP). SHIGENAGA, Shinji; 3-75-103, Yokoo 7-chome, Suma-ku, Kobe-shi, Hyogo 654-01 (JP). MURANO, Kenji; 4-15-4-202, Nagayoshinagahara, Hirano-ku, Osaka-shi, Osaka 547 (JP). MATSUDA, Hiroshi; 2-11-63-306, Toyosato, Higashiyodogawa-ku, Osaka-shi, Osaka 533 (JP). MIYAKE, Hiroshi; 86, Jodojinishidacho, Sakyo-ku, Kyoto-shi, Kyoto 606 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

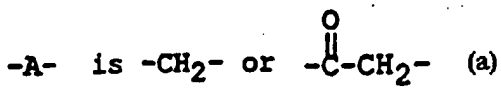
(81) Designated States: AU, CA, CN, HU, JP, KR, MX, NZ, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

**Published**
*With international search report.*

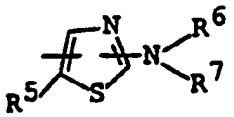
(54) Title: 1-BENZOYL-2-(INDOLYL-3-ALKYL)-PIPERAZINE DERIVATIVES AS NEUROKININ RECEPTOR ANTAGONISTS



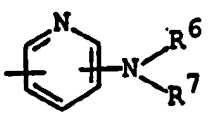
(I)



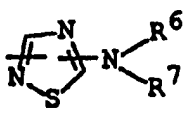
(a)



(b)



(c)



(d)

(57) Abstract

This invention relates to compounds of generic formula (I), to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament. In formula (I ), $R^1$ is trihalo(lower)alkyl, $R^2$ is trihalo(lower)alkyl, $R^3$ is indolyl(lower)alkyl, -A- is $-CH_2-$ or (a), and $-R^4$ is (b), (c) or (d) in which $R^5$ is hydrogen or lower alkoxycarbonyl, $R^6$ is hydrogen or lower alkanoyl, $R^7$ is hydrogen, lower alkyl, lower alkanoyl, lower alkoxycarbonyl, lower alkoxy(lower)alkanoyl, cyclo(lower)alkylcarbonyl, aroyl or lower alkylsulfonyl, or its pharmaceutically acceptable salt.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|---|---|---|---|---|---|
| **AM** | Armenia | **GB** | United Kingdom | **MW** | Malawi |
| **AT** | Austria | **GE** | Georgia | **MX** | Mexico |
| **AU** | Australia | **GN** | Guinea | **NE** | Niger |
| **BB** | Barbados | **GR** | Greece | **NL** | Netherlands |
| **BE** | Belgium | **HU** | Hungary | **NO** | Norway |
| **BF** | Burkina Faso | **IE** | Ireland | **NZ** | New Zealand |
| **BG** | Bulgaria | **IT** | Italy | **PL** | Poland |
| **BJ** | Benin | **JP** | Japan | **PT** | Portugal |
| **BR** | Brazil | **KE** | Kenya | **RO** | Romania |
| **BY** | Belarus | **KG** | Kyrgystan | **RU** | Russian Federation |
| **CA** | Canada | **KP** | Democratic People's Republic of Korea | **SD** | Sudan |
| **CF** | Central African Republic | | | **SE** | Sweden |
| **CG** | Congo | **KR** | Republic of Korea | **SG** | Singapore |
| **CH** | Switzerland | **KZ** | Kazakhstan | **SI** | Slovenia |
| **CI** | Côte d'Ivoire | **LI** | Liechtenstein | **SK** | Slovakia |
| **CM** | Cameroon | **LK** | Sri Lanka | **SN** | Senegal |
| **CN** | China | **LR** | Liberia | **SZ** | Swaziland |
| **CS** | Czechoslovakia | **LT** | Lithuania | **TD** | Chad |
| **CZ** | Czech Republic | **LU** | Luxembourg | **TG** | Togo |
| **DE** | Germany | **LV** | Latvia | **TJ** | Tajikistan |
| **DK** | Denmark | **MC** | Monaco | **TT** | Trinidad and Tobago |
| **EE** | Estonia | **MD** | Republic of Moldova | **UA** | Ukraine |
| **ES** | Spain | **MG** | Madagascar | **UG** | Uganda |
| **FI** | Finland | **ML** | Mali | **US** | United States of America |
| **FR** | France | **MN** | Mongolia | **UZ** | Uzbekistan |
| **GA** | Gabon | **MR** | Mauritania | **VN** | Viet Nam |

D E S C R I P T I O N

# 1-BENZOYL-2-(INDOLYL-3-ALKYL)-PIPERAZINE DERIVATIVES AS NEUROKININ RECEPTOR ANTAGONISTS

TECHNICAL FIELD

The present invention relates to new piperazine derivatives and a pharmaceutically acceptable salt thereof.

More particularly, it relates to new piperazine derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

Accordingly, one object of the present invention is to provide new and useful piperazine derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like.

Another object of the present invention is to provide a process for the preparation of said piperazine derivatives and a salt thereof.

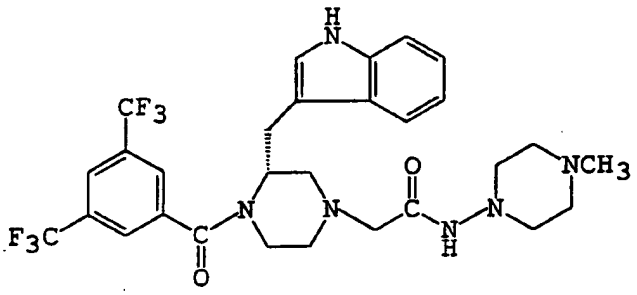
A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said piperazine derivatives and a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said piperazine derivatives or a pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis,

cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g., migraine, headache, toothache cancerous pain, back pain, etc.); and the like in human being or animals.

DISCLOSURE OF INVENTION

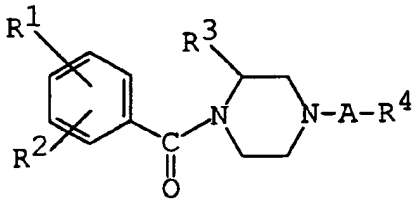
The object compound of the present invention is the compound of the following formula (I):



(I),

namely (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-4-[N-(4-methyl-1-piperazinyl)carbamoylmethyl]-piperazine, or fumaric acid salt thereof, namely (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-4-[N-(4-methyl-1-piperazinyl)carbamoylmethyl]piperazine fumarate [hereinafter referred to briefly as compound (If)].

The other object compound of the present invention can be represented by the following general formula (Ig) :



(Ig)

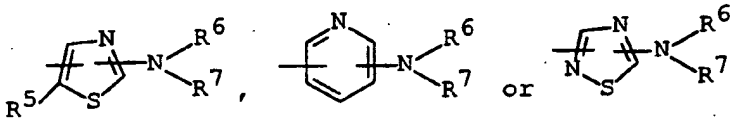
wherein

$R^1$ is trihalo(lower)alkyl,

$R^2$ is trihalo(lower)alkyl,

$R^3$ is indolyl(lower)alkyl,

-A- is $-CH_2-$ or $-\overset{O}{\overset{\|}{C}}-CH_2-$, and

-$R^4$ is 

in which

$R^5$ is hydrogen or lower alkoxycarbonyl,

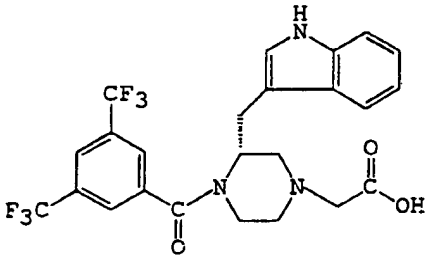
$R^6$ is hydrogen or lower alkanoyl,

$R^7$ is hydrogen, lower alkyl, lower alkanoyl, lower alkoxycarbonyl, lower alkoxy(lower)alkanoyl, cyclo(lower)alkylcarbonyl, aroyl or lower alkylsulfonyl,

or its pharmaceutically acceptable salt.

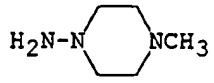
According to the present invention, the object compounds can be prepared by processes which are illustrated in the following schemes.

Process 1



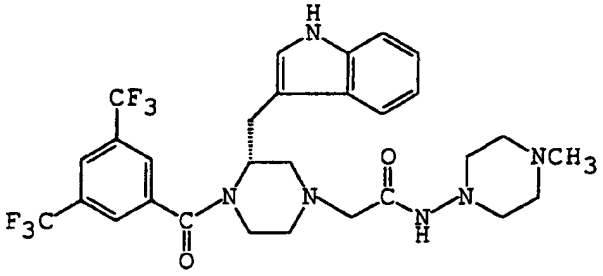
(II)

or its reactive derivative at the carboxy group or a salt thereof



(III)

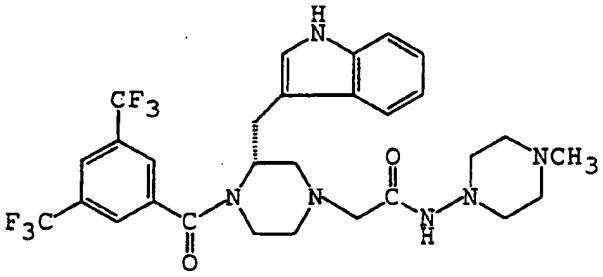
or its reactive derivative at the amino group or a salt thereof



(I)

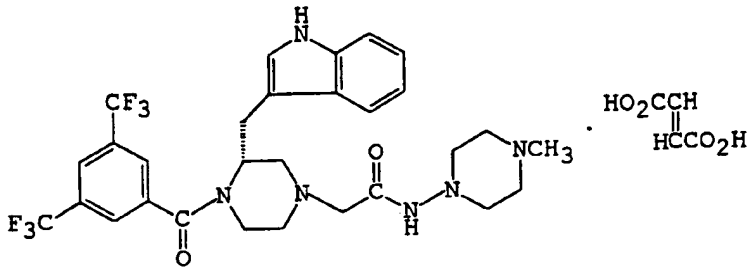
or a salt thereof

Process 2



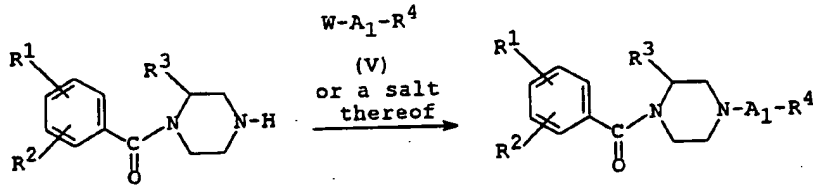
(I)

or a salt thereof other than fumaric acid salt thereof



(If)

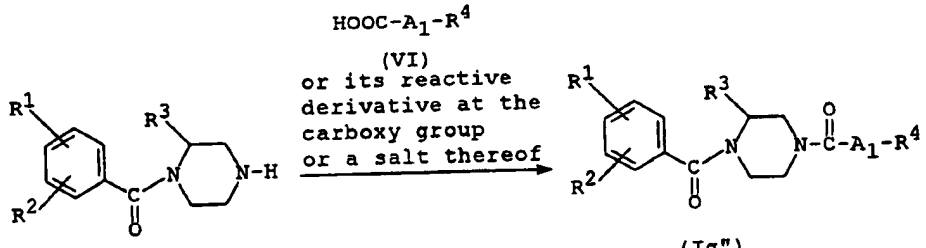
Process 3



(IV)
or its reactive derivative at the imino group or a salt thereof

(Ig')
or a salt thereof

Process 4



(IV)
or its reactive derivative at the imino group or a salt thereof

(Ig")
or a salt thereof

wherein $R^1$, $R^2$, $R^3$ and $R^4$ are each as defined above;

$-A_1-$ is $-CH_2-$; and

W is a leaving group.

Suitable salts and pharmaceutically acceptable salts of the starting and object compounds are conventional non-toxic salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "indolyl(lower)alkyl" and "lower alkylsulfonyl" is straight or branched one having 1 to 6 carbon atom(s) and may include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl and the like.

Suitable "trihalo(lower)alkyl" may include trichloromethyl, tribromomethyl, trifluoromethyl and the like.

Suitable "lower alkoxy" and "lower alkoxy moiety" in the

terms "lower alkoxycarbonyl" and "lower alkoxy(lower)alkanoyl" may include methoxy, ethoxy, isopropyloxy, butoxy and the like.

Suitable "lower alkanoyl" and "lower alkanoyl moiety" in the term "lower alkoxy(lower)alkanoyl" may include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, hexanoyl, pivaloyl and the like.

Suitable "cyclo(lower)alkyl moiety" in the term "cyclo(lower)alkylcarbonyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

Suitable "aroyl" may include benzoyl, toluoyl, naphthoyl and the like.

Suitable "leaving group" may include hydroxy, reactive group derived from hydroxy and the like.

Suitable "reactive group derived from hydroxy" may include acid residue and the like.

Suitable "acid residue" may include halogen (e.g. fluoro, chloro, bromo, iodo), acyloxy (e.g. acetoxy, tosyloxy, mesyloxy, etc.) and the like.

The Processes 1 to 4 for preparing the object compounds of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting a compound (II) or its reactive derivative at the carboxy group or a salt thereof with a compound (III) or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.

Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from the above according to the kind of the compound (II) to be used.

Suitable reactive derivative at the amino group of the compound (III) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by

reaction of the compound (III) with phosphorus trichloride or phosgene and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, 2-butanone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction, or the mixture thereof.

In this reaction, when the compound (II) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; 1-hydroxybenzotriazole; so-called Mukaiyama reagent such as 2-chloro-1-methylpyridinium iodide; 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride by itself or in combination with 1-hydroxybenzotriazole; so called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.;

or the like, or the mixture thereof.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The object compound (If) can be prepared by reacting the compound (I) or a salt thereof other than fumaric acid salt thereof with fumaric acid.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, 2-butanone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction, or the mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 3

The object compound (Ig') or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivative at the imino group or a salt thereof with the compound (V) or a salt thereof.

Suitable reactive derivative at the imino group of the compound (IV) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (IV) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IV) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide,

bis(trimethylsilyl)urea or the like;
a derivative formed by reaction of the compound (IV) with phosphorus trichloride or phosgene and the like.

This reaction is usually carried out in a solvent such as alcohol [e.g. methanol, ethanol, etc.], dichloromethane, benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

The raction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], alkali metal hydride [e.g. sodium hydride, potassium hydride, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, diisopropylethylamine, etc.], pyridine or its derivative [e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.], or the like. In case that the base to be used in liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction can be carried out under cooling, at room temperature or under warming or heating.

Process 4

The compound (Ig") or a salt thereof can be prepared by reacting a compound (IV) or its reactive derivative at the imino group or a salt thereof with a compound (VI) or its reactive derivative at the carboxy group or a salt thereof.

The reaction can be carried out in the manner disclosed in Preparation 10 or similar manners thereto.

The object compounds of the present invention have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or

Neurokinin B antagonism, and therefore are useful for treating or preventing Tachykinin-mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma, bronchitis (e.g. chronic bronchitis, acute bronchitis and diffuse panbronchiolitis, etc.), rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like;
cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like;
pains or aches (e.g. migraine, headache, cluster headache, toothache, cancerous pain, back pain, neuralgia, etc.); and the like.

Further, it is expected that the object compounds of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like, circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, Raynaud's disease, and the like; epilepsy; spastic paralysis; pollakiuria; cystitis; bladder detrusor hyperreflexia; urinary incontinence; Parkinson diseases; dementia; AIDS related dementia; Alzheimer's diseases; Down's syndrome; Huntington's chorea; carcinoid syndrome; disorders related to immune enhancement or suppression; disorders caused by Helicobacter pylori or another spiral urease-positive gram-negative bacterium; sunburn; angiogenesis or diseases caused by angiogenesis; and the like.

It is furthermore expected that the object compounds of the present invention are useful for treating or preventing chronic obstructive pulmonary diseases, particularly chronic

pulmonary emphysema; iritis; proliferative vitreoretinopathy; psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; tenalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis; mental diseases, particularly anxiety, depression, dysthymic disorders and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis; and the like.

For therapeutic purpose, the object compounds of the present invention can be used in a form of pharmaceutical preparation containing one of said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external including topical, enteral, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration. The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary

substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the object compounds will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the object compounds may be effective for treating Tachykinin-mediated diseases such as asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to illustrate the usefulness of the object compounds, the pharmacological test data of a representative compound of the present invention is shown in the following.

The following Test Compound showed more than 90% inhibition rate of $^{125}$I-BH-Substance P binding to h-$NK_1$ receptors at the concentration of 0.1 µg/ml.

Test Compound : The object compound of the Example 2

$^{125}$I-BH-Substance P Binding to h-$NK_1$ Receptors

Test Method : $^{125}$I-BH-Substance P Binding to h-$NK_1$ Receptors

(a) Crude CHO cell membrane preparation

CHO cells permanently expressing h-$NK_1$ receptors were harvested and homogenized with a Dounce homogenizer at 4°C in a buffer (0.25 M sucrose, 25 mM Tris-HCl pH 7.4, 10 mM $MgCl_2$, 1 mM EDTA, 5 µg/ml p-APMSF). The homogenate was centrifuged (500 x g, 10 minutes), and the pellet was resuspended in the same buffer, homogenized, and centrifuged. The two supernatants were combined and centrifuged (100,000 x g, 1 hour). The crude cell membranes thus isolated were resuspended in buffer (25 mM Tris-HCl pH 7.4, 10 mM $MgCl_2$,

1 mM EDTA, 5 μg/ml p-APMSF) and stored at -80°C until use.

(b) $^{125}$I-BH-Substance P binding to preparation membrane

Cell membranes (6 μg/ml) were incubated with $^{125}$I-BH-Substance P (0.1 nM) with or without test compounds in 0.25 ml of Medium 2 (50 mM Tris-HCl pH 7.4, 5 mM $MnCl_2$, 20 μg/ml chymostatin, 40 μg/ml bacitracin, 4 μg/ml leupeptin, 5 μg/ml p-APMSF, 200 μg/ml BSA) at 22°C for 90 minutes. At the end of the incubation period, the content was quickly filtered over a Wahtman GF/C glass filter (pretreated with 0.1% polyethylene imine for 3 hours prior to use) under aspiration. Each of the filters was then washed four times with 5 ml of buffer (50 mM Tris-HCl pH 7.4, 5 mM $MnCl_2$). The radioactivity was counted by using Auto Gamma counter (Packerd RIASTAR 5420A). All data presented are specific binding defined as that displaceable by 3 μM unlabeled Substance P.

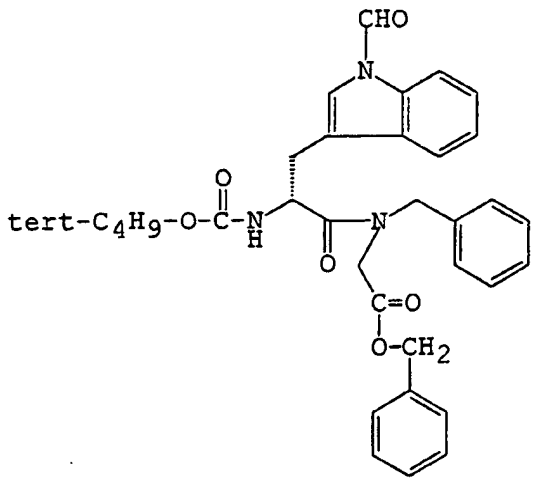
Further, the object compound of the present invention, especially the compound (If), is also superior in stability and the like.

EXAMPLES

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

- to be continued on the next page -

Preparation 1



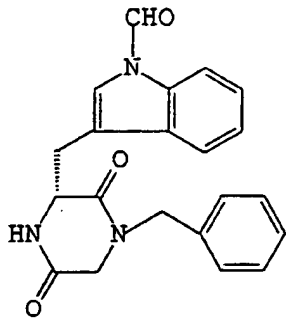
To a mixture of $N^2$-(tert-butoxycarbonyl)-$N^1$-formyl-D-tryptophan (3.99 g) and N-benzyl glycin benzyl ester hydrochloride (3.50 g) in dichloromethane (70 ml) was added triethylamine (5.85 ml) under nitrogen atmosphere. To the mixture was added 2-chloro-1-methylpyridinium iodide (3.67 g) at room temperature, and the resulting mixture was stirred for 2 hours. After the reaction was completed, dichloromethane (30 ml) and water (30 ml) were added. The organic layer was separated, washed with 0.5N hydrochloric acid (10 ml), water (10 ml), aqueous sodium bicarbonate solution (10 ml) and brine (20 ml) successively and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified on a silica gel column (140 g) eluting with a mixture of toluene and ethyl acetate (4:1) to give (2R)-N-benzyl-N-benzyloxycarbonylmethyl-2-(tert-butoxycarbonylamino)-3-(N-formyl-1H-indol-3-yl)propanamide (6.41 g) as an oil.

IR ($CHCl_3$) : 3300, 2970, 1740, 1700, 1644, 1604 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 0.89, 1.22 and 1.29 (9H, 3 s); 2.80-3.10 (2H, m); 3.95-4.25 (2H, m); 4.40-4.90 (3H, m); 4.95-5.20 (2H, m); 7.05-7.75 (15H, m); 7.98 and 8.22 (1H, 2 br s); 9.22 and 9.61 (1H, 2 br s)

MASS : 570 (M+1)

Preparation 2



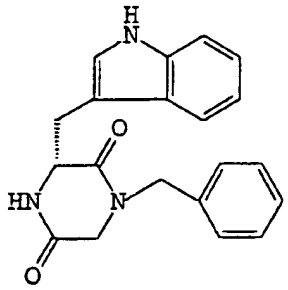

To an ice-cooled solution of the object compound of Preparation 1 (6.39 g) in dichloromethane (50 ml) was added 4N hydrogen chloride in dioxane solution (50 ml). The mixture was stirred at the same temperature for 30 minutes and at room temperature for 1 hour. After evaporation of the solvent, the residue was partitioned between dichloromethane (50 ml) and aqueous sodium bicarbonate solution (30 ml). The organic layer was separated, dried over magnesium sulfate and filtered. To the filtrate was added triethylamine (1.67 ml) at room temperature, and the mixture was stirred for 1.5 hours. After evaporation, the residue was triturated with diisopropyl ether, collected by filtration and dried to give (3R)-1-benzyl-3-(N-formyl-1H-indol-3-ylmethyl)piperazine-2,5-dione (3.93 g).

mp : 176-178°C

IR (Nujol) : 3250, 1709, 1648, 1630 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.95-3.30 and 3.35-3.70 (4H, 2 m); 4.22 (1H, d, J=14.6Hz); 4.30-4.40 (1H, m); 4.54 (1H, d, J=14.9Hz); 6.80-7.75 (9H, m); 7.95-8.50 (2H, m); 9.20 and 9.65 (1H, 2 br s)

Preparation 3



To an ice-cooled solution of the object compound of Preparation 2 (3.89 g) in a mixture of methanol (175 ml) and tetrahydrofuran (50 ml) was added aqueous 0.1N sodium hydroxide solution (108 ml). The mixture was stirred at the same temperature for 30 minutes and at room temperature for 1.5 hours. After evaporation of the solvent, the residue was extracted with dichloromethane. The organic layer was washed with water and an aqueous sodium chloride solution, and dried over magnesium sulfate. Evaporation of the solvent gave (3R)-1-benzyl-3-(1H-indol-3-ylmethyl)piperazine-2,5-dione (3.68 g).

mp : 207-208°C

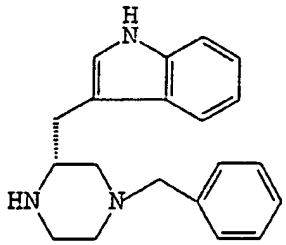
IR (Nujol) : 3402, 1650 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.68 (1H, d, J=17.2Hz); 3.04 (1H, dd, J=14.4 and 4.4Hz); 3.20-3.40 (2H, m); 4.24 (1H, s); 4.10-4.40 (2H, m); 6.75-7.60 (10H, m); 8.35

(1H, s); 10.94 (1H, s)

MASS : 334 (M+1)

Preparation 4



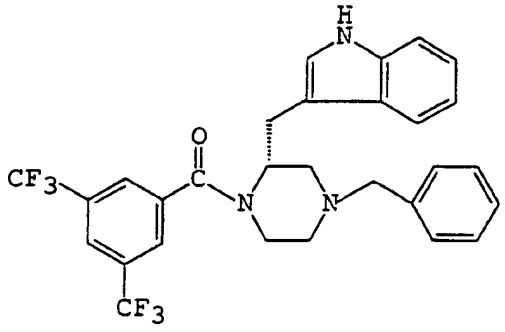
To a suspension of lithium aluminum hydride (0.77 g) in tetrahydrofuran (40 ml) was added dropwise a solution of the object compound of Preparation 3 (3.40 g) in tetrahydrofuran (40 ml) at 0°C under nitrogen atmosphere. The mixture was stirred at room temperature for 50 minutes and at refluxing temperature for 1 hour. The resulting mixture was diluted with tetrahydrofuran (60 ml) and cooled to 0°C. Water (3.0 ml) and aqueous 15% sodium hydroxide solution (0.8 ml) were added slowly. The resulting insoluble inorganic material was removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined and evaporated under reduced pressure to give (3R)-1-benzyl-3-(1H-indol-3-ylmethyl)piperazine (3.68 g) as an oil.

IR ($CHCl_3$) : 3240, 3040, 2900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.70-2.00 and 2.30-2.45 (2H, 2 m); 2.50-3.00 (7H, m); 3.25-3.60 (3H, m); 6.80-7.60 (10H, m); 10.80 (1H, s)

MASS : 306 (M+1)

Preparation 5



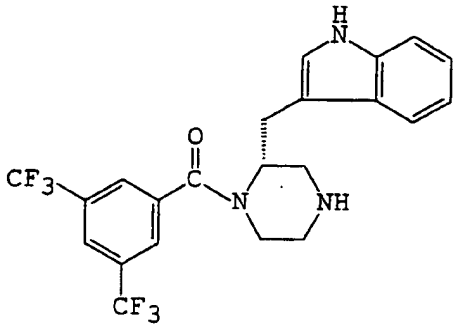
To a mixture of 3,5-bis(trifluoromethyl)benzoic acid (1.15 g) and (3R)-1-benzyl-3-(1H-indol-3-ylmethyl)piperazine (1.61 g) in dichloromethane (80 ml) was added triethylamine (1.55 ml) at room temperature under nitrogen atmosphere. 2-Chloro-1-methylpyridinium iodide (1.37 g) was added, and the mixture was stirred at room temperature for 2.5 hours. The resulting mixture was poured into water (20 ml). The organic layer was washed successively with 0.5N hydrochloric acid, water, aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. After evaporation under reduced pressure, the residue was chromatographed on silica gel with toluene - ethyl acetate (4:1) as an eluent to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine (0.87 g) as a syrup.

IR ($CHCl_3$) : 3430, 3300, 3000, 2910, 2800, 1630-1610 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.90-2.40 (2H, m); 2.70-3.90 (8H, m); 4.25-4.40 and 4.75-4.90 (1H, m); 6.50-7.45 (10H, m); 7.50-8.25 (3H, m); 10.77 (1H, s)

MASS : 546 (M+1)

Preparation 6



A mixture of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(1H-indol-3-ylmethyl)piperazine (5.20 g), ammonium formate (1.50 g) and 10% Pd charcoal (0.52 g) in ethanol (50 ml) was refluxed for 7.5 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered through Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified on a silica gel column eluting with a mixture of dichloromethane and methanol (20:1) to give (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(1H-indol-3-ylmethyl)piperazine (2.67 g) as a syrup.

IR ($CHCl_3$) : 3280, 2900, 1622 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 2.50-3.50 (9H, m); 3.6-4.8 (1H, m); 6.55-7.40 (5H, m); 7.50-8.22 (3H, m); 10.84 (1H, s)

MASS : 456 (M+1)

Preparation 7

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine (1.5 g), benzyl 2-bromoacetate (0.79 g), triethylamine (0.55 ml) and tetrahydrofuran (15 ml) was stirred overnight at room temperature. The resulting insoluble material was removed by filtration and the filtrate was concentrated under reduced

pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and methanol (30:1) to give (2R)-4-(benzyloxycarbonylmethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-piperazine (1.92 g).

$[\alpha]_D^{21}$ : -11.6° (C=1.0, MeOH)

IR (Neat) : 3600-3100, 1735, 1626, 1275, 1129, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.20-5.20 (13H, m); 6.60-8.20 (13H, m); 10.85 (1H, br s)

MASS : 604 (M+1), 454

Preparation 8

A mixture of (2R)-4-(benzyloxycarbonylmethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-piperazine (1.86 g), 10% Pd charcoal (0.186 g) and tetrahydrofuran (93 ml) was stirred for 17 hours under hydrogen gas atmosphere (1 atm). The catalyst was removed by filtration and the filtrate was concentrated. The residue was triturated with ethyl ether to give (2R)-4-(carboxymethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine (0.83 g) as a white powder.

$[\alpha]_D^{19}$ : -3.0° (C=0.5, DMF)

mp : 152-156°C

IR (Nujol) : 3600-3100, 1654, 1630, 1277, 1196, 1130 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.20-5.20 (11H, m); 6.60-8.20 (8H, m); 10.85 (1H, s)

MASS : 514 (M+1)

Preparation 9

To an ice-cooled mixture of (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]piperazine (0.3 g) and triethylamine (0.39 ml) in dimethylformamide (8 ml) was added 3-(chloromethyl)pyridine hydrochloride (0.12 g). The reaction mixture was stirred at the same temperature for 30

minutes and then at room temperature for 2 hours. Additional triethylamine (0.39 ml) and 3-(chloromethyl)pyridine hydrochloride (0.12 g) were added and the resulting mixture was stirred overnight. The reaction mixture was filtered and the filtrate was concentrated and subjected to a chromatography on a silica gel eluting with a mixture of toluene and ethyl acetate (5:1). The eluent was treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(pyridin-3-ylmethyl)piperazine dihydrochloride.

mp : 164-168°C

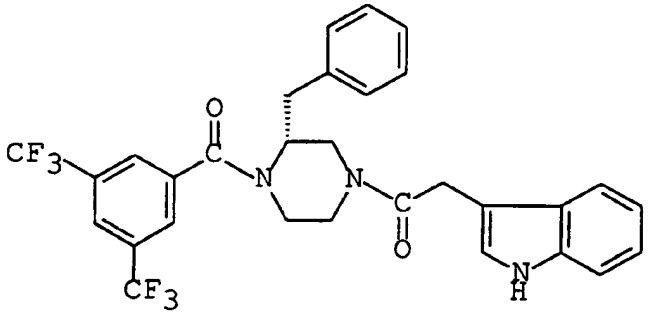
$[\alpha]_D^{25}$ : +9.1° (C=1.0, MeOH)

IR (Nujol) : 3700-3100, 2700-2000, 1630, 1270, 1120, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.80-5.40 (11H, m); 6.85-6.90 (1H, m); 7.10-7.40 (4H, m); 7.46 (1H, s); 7.75 (1H, s); 7.90-8.00 (1H, m); 8.19-8.23 (1H, m); 8.66-8.70 (1H, m); 8.88-8.91 (1H, m); 9.09 (1H, s)

MASS : 508 (M+1) (free)

Preparation 10



To a stirred mixture of (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]piperazine (0.3 g) and 2-(1H-indol-3-yl)acetic acid (0.13 g) in dichloromethane (8 ml) containing triethylamine (0.25 ml) was added 2-chloro-1-methylpyridinium iodide (0.22 g) at room temperature under nitrogen atmosphere. After being stirred for 5 hours, the reaction mixture was diluted with dichloromethane and washed with 0.1N hydrochloric acid, aqueous saturated sodium bicarbonate solution and brine, and dried over magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel using chloroform-methanol (50:1) as eluent to give (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[2-(1H-indol-3-yl)acetyl]piperazine (0.34 g) as a white powder.

mp : 201-210°C

$[\alpha]_D^{27}$ : +27.6° (C=1.0, MeOH)

IR (Nujol) : 3270, 1630, 1276, 1115, 900, 737 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.60-5.00 (11H, m); 6.70-7.70 (12H, m); 8.10-8.20 (1H, m); 10.85-11.10 (1H, m)

MASS : 574 (M+1), 417

Preparation 11

To a solution of (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(1H-indol-3-ylmethyl)piperazine (0.1 g) in dichloromethane (10 ml) was added 4N hydrogen chloride in dioxane solution (0.05 ml) at 0°C. The resulting mixture was stirred at the same temperature for 50 minutes and then concentrated under reduced pressure. The obtained powder was collected by filtration and washed with ethyl ether to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine hydrochloride (0.1 g).

IR (Nujol) : 3340, 1648 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.9-3.9 (8H, m); 3.9-5.2 (1H, m); 6.57-7.50 (5H, m); 7.50-8.30 (3H, m); 9.40-10.00 (2H, m); 10.96 (1H, s)

MASS : 456 (M+1) (free)

Preparation 12

To a stirred mixture of (2R)-4-(2-aminoethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)piperazine dihydrochloride (110 mg), triethylamine (0.2 ml) in dichloromethane (10 ml) was added methanesulfonyl chloride (0.1 ml) at 0°C. After stirring for 1 hour, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed successively with aqueous saturated sodium bicarbonate solution and brine, and dried. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on a silica gel eluting with a mixture of dichloromethane and methanol (40:1) and treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-(mesylamino)ethyl]piperazine hydrochloride (50 mg).

mp : >220°C

$[\alpha]_D^{22}$ : +0.2° (C=0.5, DMF)

IR (Nujol) : 3350, 2700-2400, 1645, 1500, 1450, 1380 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.10 and 2.18 (6H, 2 s); 2.7-5.2 (17H, m); 6.6-7.7 (5H, m); 8.1-8.2 (1H, m); 11.05-11.4 (1H, m)

MASS : 566 (M+1) (free)

Example 1

To a stirred solution of (2R)-4-(carboxymethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-piperazine (1 g) in dry dimethylformamide (10 ml) was added 1-hydroxybenzotriazole (0.29 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.41 g) at room temperature. After stirring for 15 minutes at room temperature, 1-amino-4-methylpiperazine (320 mg) was

added and further stirred for 5 hours at the same temperature. The reaction mixture was poured into a solution of sodium hydrogencarbonate (1.8 g) in water (100 ml) and extracted three times with 20 ml portions of ethyl acetate. The organic layers were combined and washed with brine (30 ml). The organic layer was dried over magnesium sulfate and filtered and the solvent was removed by rotary evaporator. The crude product was purified by chromatography (silica gel, dichloromethane:methanol, 5:1) to afford (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-4-[N-(4-methyl-1-piperazinyl)carbamoylmethyl]-piperazine (0.94 g) as a yellowish powder.

IR (Nujol) : 3180, 1680, 1630, 1276, 1170, 1130, 1005, 897 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.16 (3H, s); 2.0-5.0 (19H, m); 6.6-8.2 (8H, m); 8.47, 8.77 (1H, 2 s); 10.85 (1H, s)

Example 2

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-4-[N-(4-methyl-1-piperazinyl)carbamoylmethyl]-piperazine (10.89 g) and fumaric acid (2.07 g) were dissolved in ethanol (50 ml) at 70°C. After cooling, the resulting solution was concentrated under reduced pressure to give a powder (13.18 g). The powder (9.68 g) was dissolved in 2-butanone (194 ml) at reflux temperature and the solution was allowed to stir at room temperature to afford crystals, which was collected by filtration and dried to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-4-[N-(4-methyl-1-piperazinyl)carbamoylmethyl]piperazine fumarate (7.94 g).

mp : 169.5-171°C

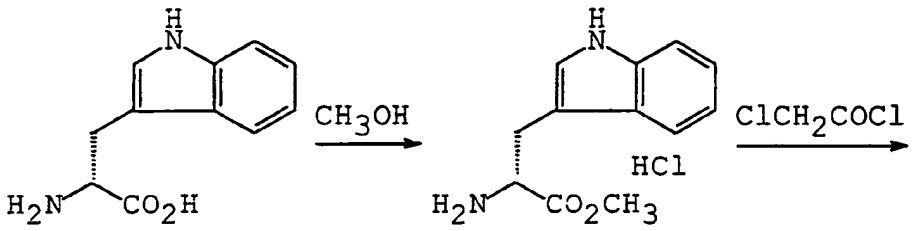
IR (Nujol) : 3220, 1700, 1653, 1630, 1275, 1217, 1168, 1122, 979, 894, 730 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.23, 2.26 (3H, 2 s); 2.10-4.93

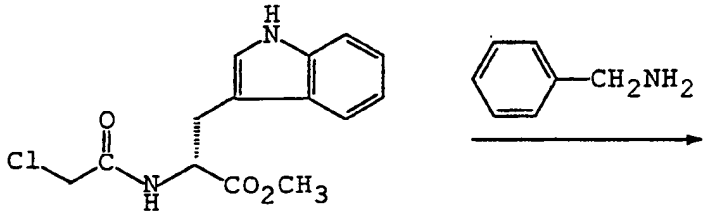
(19H, m); 6.60 (2H, s); 6.54-8.23 (8H, m); 8.50, 8.85 (1H, 2 s); 10.85 (1H, s)

Example 3

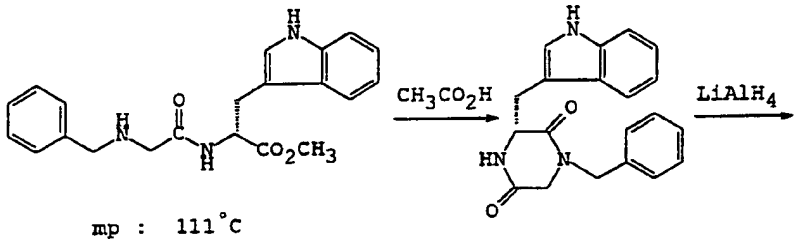
Compound (If), namely (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(1H-indol-3-ylmethyl)-4-[N-(4-methyl-1-piperazinyl)carbamoylmethyl]piperazine fumarate was also obtained according to the following scheme.



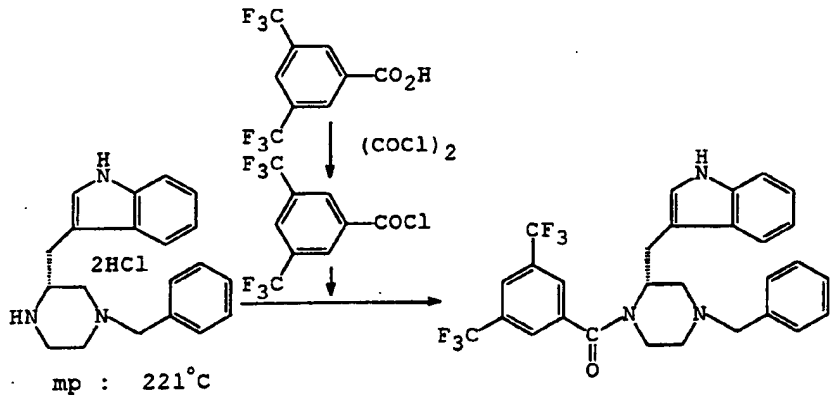

mp : 224-225°C (dec)



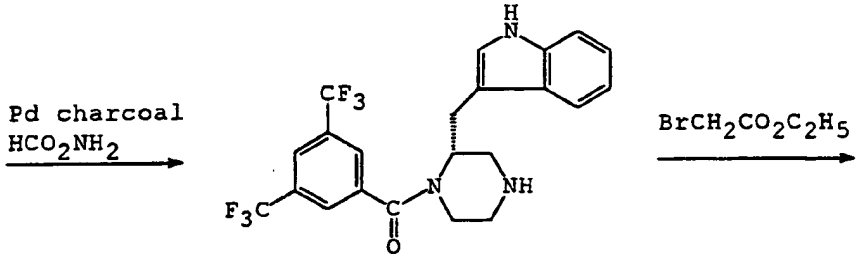

mp : 243°C (dec)

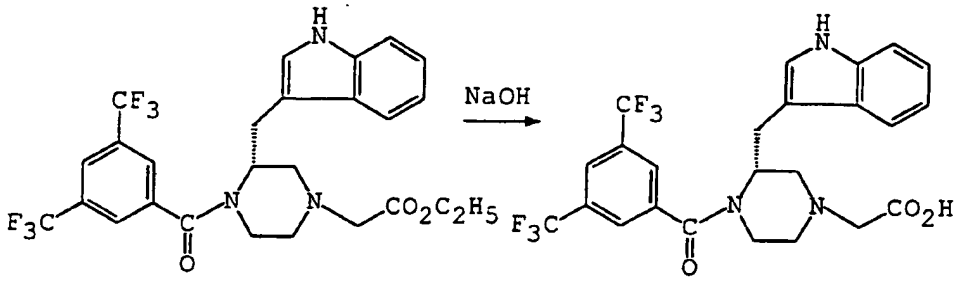


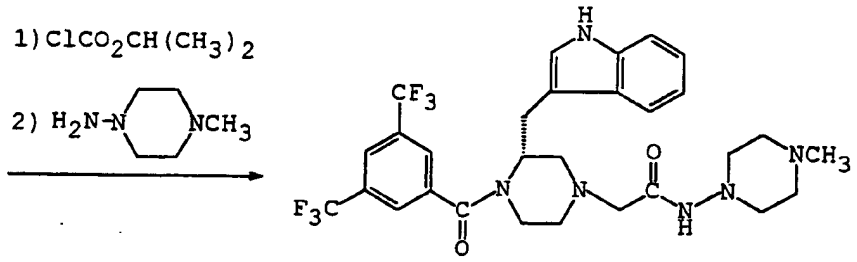

mp : 111°C



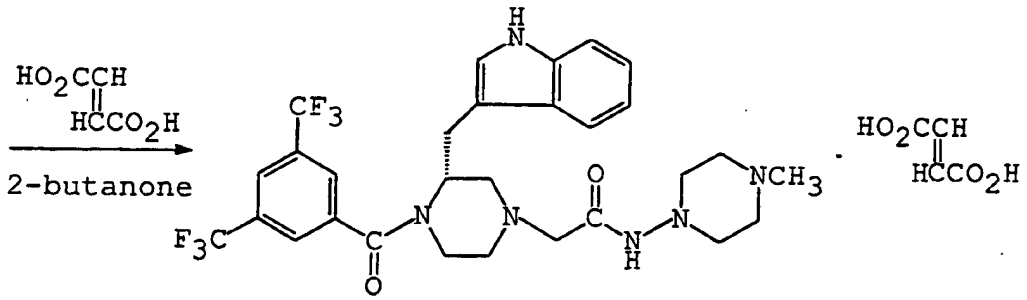

mp : 221°C






Compound (I)




Compound (If)

Example 4

A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine (120 mg), 4-chloromethyl-2-(2-methoxyethylcarbonylamino)thiazole (70 mg) and powdered sodium hydrogen carbonate (27 mg) in dry dimethylformamide was stirred for 5 hours and 20 minutes at 60°C. The reaction mixture was powered into water and the resulting precipitate was collected by filtration. The crude product was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and methanol (30:1). The eluate was evaporated under reduced pressure and treated with 17.6% hydrogen chloride in ethanol (0.12 ml) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)-4-[[2-(3-methoxypropanoylamino)thiazol-4-yl]methyl]piperazine hydrochloride (140 mg).

$[\alpha]_D^{22}$ : -34.0° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2750-2000, 1635, 1275, 1130, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.60-5.20 (18H, m); 6.60-8.21 (9H, m); 10.90-11.00 (1H, m); 11.20-12.00 (1H, m); 12.19 (1H, s)

MASS : 654 (M+1) (free)

Example 5

The following piperazine derivatives (Table 1) were prepared by the similar manner to that of the each Example No. or Preparation No. defined in the "Process" column. The physical properties of the object compounds are shown after the table.

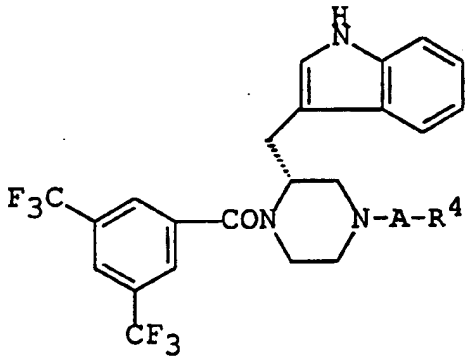


Table 1

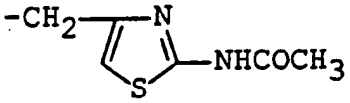
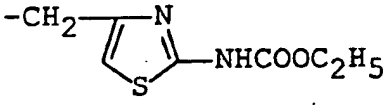
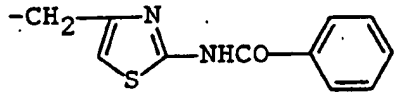
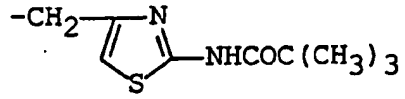
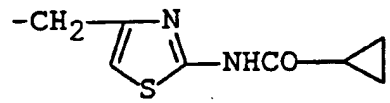
| Example No. | Object Compounds | | Starting Compound | Process |
|---|---|---|---|---|
| | -A-$R^4$ | Salt | | |
| 5-1) |  | HCl | Pr.(Preparation) 6 | Ex. 4 |
| 5-2) |  | HCl | Pr. 6 | Ex. 4 |
| 5-3) |  | HCl | Pr. 6 | Ex. 4 |
| 5-4) |  | HCl | Pr. 6 | Ex. 4 |
| 5-5) |  | HCl | Pr. 6 | Ex. 4 |

Table 1 (continued)

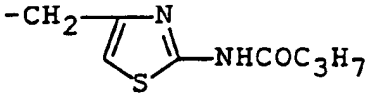
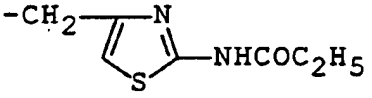
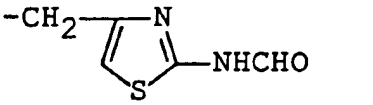
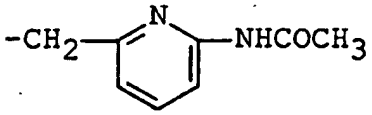
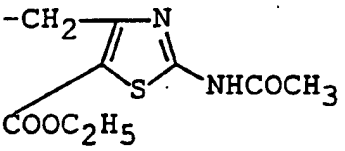
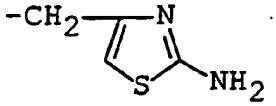
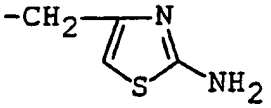
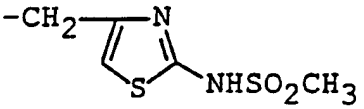
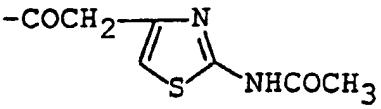
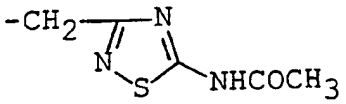
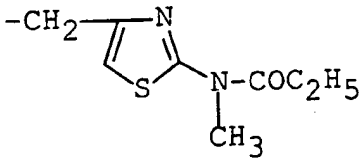
| Example No. | Object Compounds | | Starting Compound | Process |
|---|---|---|---|---|
| | -A-$R^4$ | Salt | | |
| 5-6) |  | HCl | Pr. 6 | Ex. 4 |
| 5-7) |  | HCl | Pr. 6 | Ex. 4 |
| 5-8) |  | HCl | Pr. 6 | Ex. 4 |
| 5-9) |  | 2HCl | Pr. 6 | Ex. 4 |
| 5-10) |  | HCl | Pr. 6 | Ex. 4 |
| 5-11) |  | - | Pr. 6 | Pr. 9 |
| 5-12) |  | 2HCl | Ex.5-11) | Pr.11 |
| 5-13) |  | HCl | Ex.5-11) | Pr.12 |
| 5-14) |  | - | Pr. 6 | Pr.10 |

Table 1 (continued)

| Example No. | Object Compounds -A-$R^4$ | Salt | Starting Compound | Process |
|---|---|---|---|---|
| 5-15) |  | HCl | Pr. 6 | Ex. 4 |
| 5-16) |  | HCl | Pr. 6 | Ex. 4 |

Physical properties of the compounds of the Example 5 :

Example 5-1)

mp : 185-189°C

$[\alpha]_D^{24}$ : 30.2° (C=0.5, MeOH)

IR (Nujol) : 3660-3100, 2800-2000, 1635, 1545, 1276, 1183, 1130, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.36-5.10 (14H, m); 6.59-8.22 (10H, m); 10.90-11.00 (1H, m); 12.15 (1H, s)

MASS : 610 (M+1) (free), 456

Example 5-2)

$[\alpha]_D^{22}$ : -33.4° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2800-2000, 1715, 1635, 1555, 1274, 1130, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.25 (3H, t, J=7.1Hz); 2.73-5.10 (13H, m); 6.60-8.30 (9H, m); 10.90-11.00 (1H, m); 11.81 (1H, br s)

MASS : 640 (M+1) (free), 456

Example 5-3)

$[\alpha]_D^{22}$ : -42.0° (C=0.5, MeOH)

IR (Nujol) : 3600-3100, 2750-2000, 1635, 1540, 1277,

1175, 1130 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.73-5.20 (11H, m); 6.59-8.21 (14H, m); 10.90-11.00 (1H, m); 12.69 (1H, s)

MASS : 672 (M+1) (free), 456

Example 5-4)

$[\alpha]_D^{22}$ : -24.2° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2750-2000, 1635, 1540, 1276, 1170, 1129, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.23 (9H, s); 2.73-5.10 (11H, m); 6.50-8.20 (9H, m); 10.80-11.00 (1H, m); 11.84 (1H, s)

MASS : 652 (M+1) (free), 456

Example 5-5)

$[\alpha]_D^{22}$ : -35.8° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2750-2000, 1635, 1540, 1276, 1170, 1130, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 0.80-1.00 (4H, m); 1.90-2.00 (1H, m); 2.73-5.15 (11H, m); 6.60-8.21 (9H, m); 10.90-11.00 (1H, m); 12.43 (1H, m)

MASS : 636 (M+1) (free), 456

Example 5-6)

$[\alpha]_D^{22}$ : -30.4° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2750-2000, 1635, 1542, 1275, 1170, 1131, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 0.89 (3H, t, J=7.4Hz); 1.56-1.67 (2H, m); 2.40-2.50 (2H, m); 2.73-5.15 (11H, m); 6.56-8.21 (9H, m); 10.90-10.94 (1H, m); 12.12 (1H, s)

MASS : 638 (M+1) (free)

Example 5-7)

$[\alpha]_D^{22}$ : -34.0° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2750-2000, 1635, 1543, 1277, 1170, 1130, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.08 (3H, t, J=7.4Hz); 2.43-2.50 (2H, m); 2.73-5.15 (11H, m); 6.55-8.21 (9H, m); 10.90-10.94 (1H, m); 12.11 (1H, s)

MASS : 624 (M+1) (free)

Example 5-8)

$[\alpha]_D^{22}$ : -15.2° (C=0.5, MeOH)

IR (Nujol) : 3600-3100, 2750-2000, 1635, 1278, 1172, 1130, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.73-5.20 (11H, m); 6.60-8.52 (11H, m); 10.94 (1H, s)

MASS : 596 (M+1) (free), 456

Example 5-9)

$[\alpha]_D^{22}$ : -20.6° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2750-2000, 1635, 1276, 1170, 1129, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.09 (3H, s); 2.73-5.20 (11H, m); 6.60-8.20 (11H, m); 10.46 (1H, s); 10.91 (1H, s)

MASS : 604 (M+1) (free)

Example 5-10)

$[\alpha]_D^{22}$ : -13.0° (C=0.5, MeOH)

IR (Nujol) : 3650-3050, 2750-2000, 1685, 1636, 1524, 1275, 1130, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.31 (3H, t, J=6.5Hz); 2.24 (3H, s); 2.73-5.20 (13H, m); 6.66-8.25 (8H, m); 10.94 (1H, s), 12.71 (1H, s)

MASS : 682 (M+1) (free)

Example 5-11)

$[\alpha]_D^{18}$ : -20.8° (C=0.5, MeOH)

IR (Neat) : 3700-3000, 1615, 1515, 1272, 1125,

900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.00-5.00 (13H, m); 6.38-8.20 (9H, m); 10.80 (1H, s)

MASS : 568 (M+1), 456

Example 5-12)

$[\alpha]_D^{22}$ : -10.4° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2750-2000, 1635, 1277, 1130 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 3.00-5.20 (11H, m); 6.60-8.30 (11H, m); 10.95 (1H, s)

MASS : 568 (M+1) (free), 456

Example 5-13)

$[\alpha]_D^{22}$ : -31.8° (C=0.5, MeOH)

IR (Nujol) : 3270, 2750-2000, 1637, 1531, 1279, 1124, 964 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.73-5.15 (14H, m); 6.60-8.25 (10H, m); 10.89 (1H, s)

MASS : 646 (M+1) (free), 568, 456

Example 5-14)

$[\alpha]_D^{23}$ : 11.8° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 1625, 1543, 1275, 1130 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.09-2.11 (3H, m); 2.52-5.00 (11H, m), 6.63-8.20 (9H, m); 10.85 (1H, s); 12.07 (1H, s)

MASS : 638 (M+1), 456

Example 5-15)

$[\alpha]_D^{18}$ : -51.6° (C=0.5, MeOH)

IR (Nujol) : 3650-3100, 2750-2000, 1634, 1540, 1274, 1170, 1127, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.31 (3H, s); 2.73-5.35 (11H, m); 6.63-8.25 (8H, m); 10.94-11.00 (1H, m); 13.20 (1H,

s)

MASS : 611 (M+1) (free)

Example 5-16)

$[\alpha]_D^{22}$ : -23.4° (C=0.5, MeOH)

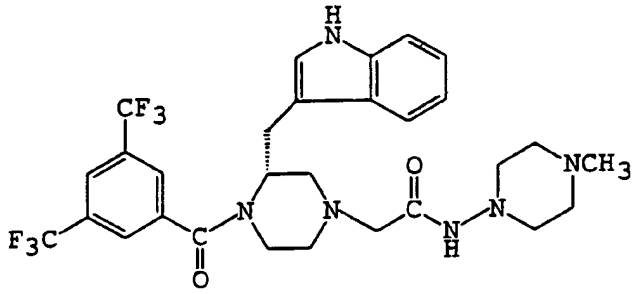
IR (Nujol) : 3650-3000, 2750-2000, 1620, 1274, 1175, 1128, 900 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.10 (3H, t, J=7.2Hz), 2.60-5.10 (16H, m); 6.50-8.21 (9H, m); 10.91 (1H, s); 11.50-11.90 (1H, br s)

MASS : 638 (M+1) (free)

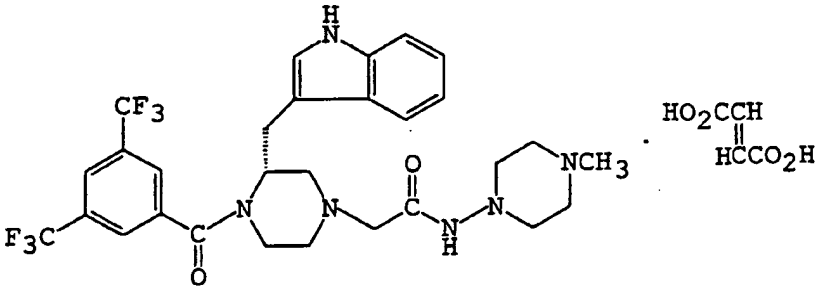
CLAIMS

1. A compound of the formula :

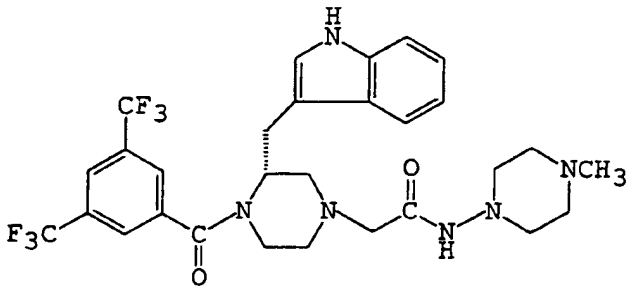


or fumaric acid salt thereof.

2. The compound of claim 1, which is the compound of the formula :

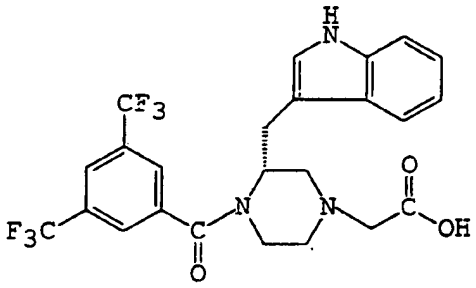


3. A process for preparing a compound of the formula :

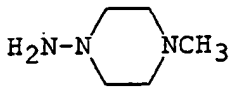


or fumaric acid salt thereof,
which comprises

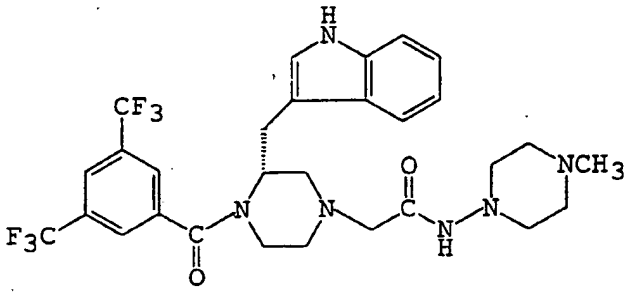
(1) reacting a compound of the formula :



or its reactive derivative at the carboxy group
or a salt thereof with a compound of the formula :

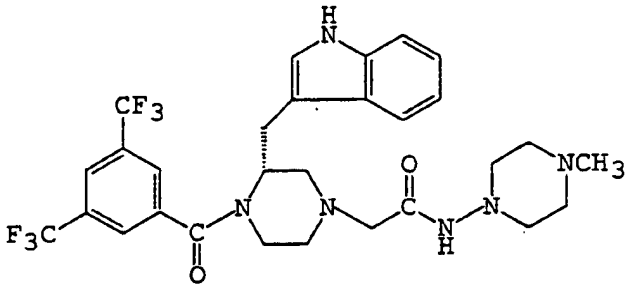


or its reactive derivative at the amino group or a salt thereof to give a compound of the formula :

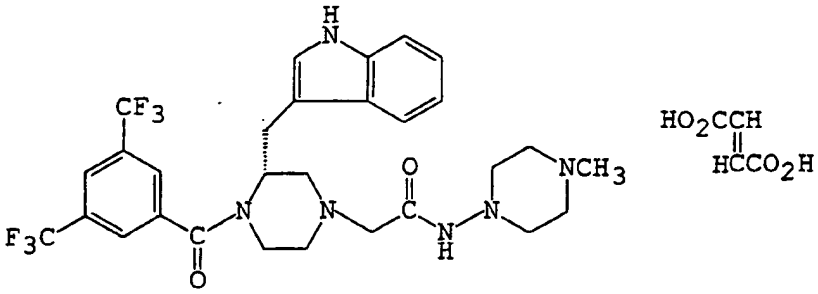


or fumaric acid salt thereof, or

(2) reacting a compound of the formula :



or a salt thereof other than fumaric acid salt thereof with fumaric acid to give a compound of the formula :



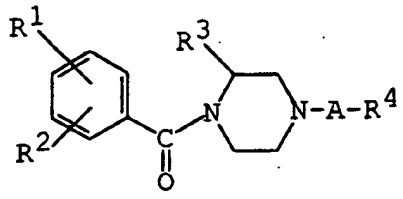
4. A pharmaceutical composition comprising a compound of claim 1 as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

5. A method for treating or preventing Tachykinin-mediated diseases which comprises administering an effective amount of a compound of claim 1 to human being or animals.

6. A compound of claim 1 for use as a medicament.

7. Use of a compound of claim 1 for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.

8. A compound of the following general formula :



wherein

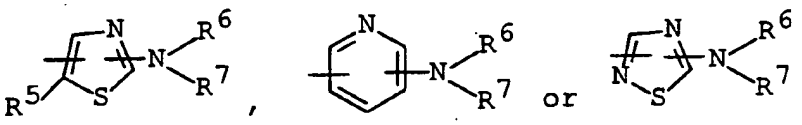
$R^1$ is trihalo(lower)alkyl,

$R^2$ is trihalo(lower)alkyl,

$R^3$ is indolyl(lower)alkyl,

-A- is $-CH_2-$ or $-\overset{O}{\overset{\|}{C}}-CH_2-$ , and

$-R^4$ is



in which

$R^5$ is hydrogen or lower alkoxycarbonyl,

$R^6$ is hydrogen or lower alkanoyl,

$R^7$ is hydrogen, lower alkyl, lower alkanoyl, lower alkoxycarbonyl, lower alkoxy(lower)alkanoyl, cyclo(lower)alkylcarbonyl, aroyl or lower alkylsulfonyl,

or its pharmaceutically acceptable salt.

# INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/JP 96/01335

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/06 C07D417/14 C07D401/14 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | EP,A,0 655 442 (FUJISAWA PHARMACEUTICAL CO) 31 May 1995<br>see the whole document | 1-8 |
| A | EP,A,0 411 150 (OTSUKA PHARMA CO LTD) 6 February 1991<br>see the whole document | 1-8 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 July 1996 | 19. 07 96 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | Kissler, B |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 96/01335

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0655442 | 31-05-95 | AU-B- | 7911194 | 08-06-95 |
| | | CA-A- | 2136712 | 30-05-95 |
| | | CN-A- | 1107149 | 23-08-95 |
| | | HU-A- | 71348 | 28-11-95 |
| | | JP-A- | 7242641 | 19-09-95 |
| | | ZA-A- | 9409228 | 01-08-95 |
| | | BR-A- | 9500539 | 31-10-95 |
| EP-A-0411150 | 06-02-91 | JP-A- | 3220188 | 27-09-91 |
| | | CN-A,B | 1049155 | 13-02-91 |
| | | WO-A- | 9009380 | 23-08-90 |
| | | US-A- | 5238938 | 24-08-93 |
| | | JP-A- | 3173883 | 29-07-91 |